THORACIC

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Contents

Radiological Staging in Thoracic Oncology

Professor Lyburn

The most important prognostic indicator in lung cancer is the extent of disease. The Union Internationale Contre le Cancer (UICC) and the American Joint Committee for Cancer Staging (AJCC) developed the tumour, node, and metastases (TNM) staging system which attempts to define those patients who might be suitable for radical surgery or radical radiotherapy from the majority who will only be suitable for palliative measures.

Imaging techniques continue to advance, but staging is often not definitive. There may be difficulties: in defining the extent of primary tumour with the presence of collapsed or consolidated lung leading to overestimation of tumour size; assessing extent of contact or involvement with major vessels, the pleura or the pericardium; identifying small malignant nodes; distinguishing reactive from malignant lymphadenopathy and in assigning significance to pulmonary nodules and ground glass opacities.

The main imaging modality in staging thoracic malignancies is multi-slice CT. It may assess the primary lesion, nodes (by size criteria) and sites of potential metastatic disease including the liver, adrenal glands and skeleton in the region imaged. MRI may be used in the assessment of superior sulcus tumours to assess for local invasion.

FDG PET-CT is now used for staging all patients with thoracic malignancy being considered for surgery or radical treatment to assess for distant metastases.

The pooled sensitivity and specificity of CT for identifying mediastinal lymph node metastases are 51% and 85% respectively and for PET scanning 74% and 85% respectively - because of the potential of under or overstaging, confirmation of the status of mediastinal nodes is recommended.

Ultrasound can assess potential chest wall involvement and may be used to direct FNA of upper mediastinal or cervical nodes. Transbronchial or transoesophageal endoluminal ultrasound may direct sampling of nodes and other lesions.

Multislice CT and FDG PET/CT have increasing roles in monitoring response to treatment in attempted downstaging pre surgery, diagnosing recurrent tumour and identifying the complications of treatment.

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SURGICAL STAGING IN THORACIC ONCOLOGY

E Bishay

Rational treatment decisions and ultimate prognosis of patients with lung cancer depend largely on the stage of disease at the time of diagnosis.

Surgical or invasive staging techniques will always be required as long as radiological and less invasive techniques are not 100% sensitive or specific in the pre-operative identification of patients most likely to benefit from pulmonary resection. This applies to all three components of TNM staging and no individual should be denied the chance of curative resection based on radiological or clinical findings alone.

The routine use of positron emission tomography (PET) scanning has redefined the indications for invasive staging of the mediastinum for the detection of N2 nodal involvement. Invasive staging procedures can be omitted in patients with small peripheral tumours and negative mediastinal PET images. However, in case of central tumours, PET hilar N1 disease, low fluorodeoxyglucose uptake of the primary tumour and lymph nodes ≥ 16 mm on CT scan, invasive staging remains indicated. PET positive mediastinal findings should always be cyto-histologically confirmed. The use of PET scans as applied to the M stage often requires cyto-histologically confirmation of distant sites of involvement.

Trans-bronchial needle aspiration (TBNA), ultrasound-guided bronchoscopy with fine needle aspiration (EBUS-FNA) and endoscopic esophageal ultrasound-guided fine needle aspiration (EUS-FNA) are new techniques that provide cyto-histological diagnosis and are minimally invasive. Their specificity is high but the negative predictive value is low. Because of this, if they yield negative results, an invasive surgical technique is indicated. They are particularly useful in restaging the mediastinum following neoadjuvant down-staging.

Bronchoscopy

Indications: Endo-bronchial T status of central tumours.

Rule out synchronous tumours in other parts of the bronchial tree.

Vocal cord involvement signifies T4.

Mediastinoscopy

Indications: Access to stations 1, 2, 4, and 7.

Ideally 2R, 2L, 4R, 4L, and 7 nodal stations should all be explored with a lesser but yet acceptable standard of 4R, 4L, and 7 to reduce the likelihood of false negative results. Also used to evaluate proximal main bronchi and medially based right tumours.

Sensitivity = 81% (TP/TP+FN), Specificity = 100 (TN/TN+FP), NPV (TN/TN+FN) =91%.

Complications: Morbidity 1-3%. Mortality 0.08%.

Mediastinotomy (Chamberlain incision)

Used alone or in combination with Mediastinoscopy.

Indications: Evaluation of left nodal stations 5 & 6, central tumours close to A-P window, appropriate T4 (Pericardial involvement) staging on right.

Sensitivity 80-85% (TP/TP+FN), Specificity =100 (TN/TN+FP)

Video Assisted Thoracic Surgery

Indications: T status in large tumours where CT can not accurately differentiate between contact and invasion. Assessment of pleural effusions and involvement (T4) including cytological confirmation.

Access to stations 5 and 6 on left and other N2 nodes not amenable to Mediastinoscopy (8, and 9).

Thoracotomy

Indications: Final and yet important staging tool ideally when all other attempts have been exhausted. During resection, thorough intra-operative staging is essential for prognosis and need for adjuvant therapy.

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Introduction

Staging of Lung Cancer: the European Perspective

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Staging of malignant tumours, as we understand it today, was a European initiative. Pierre Denoit (1912-1990), a surgical oncologist at Gustave-Roussy Institute in Paris, first started using the tumour, node, metastasis (TNM) classification system to describe the anatomic extent of disease. (1) Later on, the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) adopted this system. For lung cancer, however, the big push came from the United States of America with Clifton Mountain, (2) whose database served several editions and revisions of the TNM classification till the 6th edition.

In 1996, another European, Mr. Peter Goldstraw, a thoracic surgeon from the Royal Brompton Hospital, London, UK, lead the initiative to collect a large, international database, within the International Association for the Study of Lung Cancer (IASLC). He was the first Chairman of the IASLC International Staging Committee, and lead all the work of the committee resulting in several data-based recommendations to modify the 6th edition of the TNM classification, that were fully accepted by the UICC and the AJCC. The result was the revised 7th edition, the text of which is identical in the staging manuals of the IASLC, the UICC (3) and the AJCC (4). Nearly 60% of the over 100,000 cases registered in the IASLC database were from European institutions, (5) which gives evidence of the interest of the continent in lung cancer staging.

In the practical assessment of the anatomic extent of lung cancer, the European Society of Thoracic Surgeons (ESTS) made an important contribution with two guidelines on intraoperative nodal staging (6) and preoperative mediastinal staging. (7) These ESTS guidelines are often quoted, and the latter has been recently validated prospectively. (8) The guidelines on intraoperative staging favour systematic nodal dissection over other less rigorous procedures of nodal assessment. The guidelines on preoperative mediastinal staging recommend pathological confirmation of abnormalities seen on computed tomography or positron emission tomography scans, both at staging and at restaging after induction therapy. This confirmation is commonly performed by mediastinoscopy, but, if available, transbronchial needle aspiration or ultrasound-guided bronchoscopy and oesophagoscopy with fine needle aspiration can be alternative

procedures: if they yield a positive result, it may be enough to start a multidisciplinary treatment protocol, but if the result is negative for malignancy, mediastinoscopy is recommended, because the negative predictive value of endoscopies still is too low to make further therapeutic decisions based on it. With these guidelines, the ESTS, the largest organization of general thoracic surgeons in the world, favours staging with the highest evidence: that provided by pathological confirmation of disease extension, both preoperatively and intraoperatively.

The Prospective Phase of the IASLC Staging Project began in 2009 in order to revise the 8th edition of the TNM classification due to be published in 2016. Again, Europe is taking the lead with 75% of the nearly 4000 cases prospectively registered on line coming from European institutions.

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STAGE SPECIFIC LUNG CANCER SURGERY

Mr. D. Waller

There have been changes to the staging system with reclassification of T stage on basis of tumour size, other nodules and the presence of pleural effusion.

Stage I (tumour <7cm, N0)

“Lobectomy is the gold standard treatment”. This statement may be challenged in cases of stage Ia cancer or in patients with limited pulmonary function. In these cases an anatomical segmentectomy with lymph node dissection is an acceptable alternative.

Stage II (any T size N1, Tumour > 7cm, chest wall, mediastinal pleura N0)

Pneumonectomy is a disease in itself

Extended lung resections i.e bronchoplastic and angioplastic sleeve resections should be employed to avoid pneumonectomy.

T3 N0/1

Chest wall invasion is not a contraindication to resection. En-bloc rib resection and reconstruction is the treatment of choice.

Satellite nodules in the same lobe as the primary (now T3) should be resected.

Stage IIIB : T4 N0/1

Local invasion – in rare circumstances T4N0 tumours can be primarily resected with SVC / L atrial wall or vertebra.

Ipsilateral nodules – the 7th revision downstaged ipsilateral nodules in a separate lobe to the primary from M1 to T4. In these rare circumstances sublobar resection is preferable to pneumonectomy.

Stage IV

Oligometastatic disease – in rare cases where a stage I/II tumour presents with an isolated brain or adrenal metastasis initial metastasectomy can be justified if subsequent complete pulmonary resection is possible.

Stage IIIA (N2 disease)

N2 disease represents both a spectrum of disease and the interface between surgical and non-surgical treatment of lung cancer

Evidence from the staging revision suggests that single zone N2 disease has a similar prognosis to multizone N1 disease and therefore arguably should be treated primarily by surgery

Evidence from Intergroup 0139/EORTC 08941 trials suggests that multizone or unresectable N2 disease should be treated primarily by chemoradiotherapy. There may be a role for surgery if N2 is downstaged to N0 and lobectomy is possible but pneumonectomy is avoidable.

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Management of stage III lung cancer – thoracic debate

Paul E. Van Schil, MD

The role of surgery in stage IIIA-N2 non-small cell lung cancer (NSCLC) remains controversial. Most important prognostic factors are mediastinal downstaging and complete surgical resection. Different restaging techniques exist to evaluate response after induction therapy. In contrast to imaging or functional studies, invasive techniques as remediastinoscopy provide pathological evidence of response after induction therapy. An alternative approach consists of the use of minimally invasive staging procedures as endobronchial or endoscopic oesophageal ultrasound to obtain an initial proof of mediastinal nodal involvement. Mediastinoscopy is subsequently performed after induction therapy to evaluate response.

Stage IIIA-N2 NSCLC represents a heterogeneous spectrum of locally advanced disease and different subsets exist. When N2 disease is discovered during thoracotomy after negative, careful preoperative staging a resection should be performed if this can be complete. Postoperative radiotherapy will decrease local recurrence rate but will not improve overall survival. Adjuvant chemotherapy increases survival and is presently recommended in these cases. Most patients with pathologically proven, potentially resectable N2 disease detected during preoperative work-up will be treated by induction therapy followed by surgery or radiotherapy. Surgical resection may be recommended in those patients with proven mediastinal downstaging after induction therapy who can preferentially be treated by lobectomy. Unresectable, bulky N2 disease is mostly treated with combined chemoradiotherapy.

In stage IIIB primary surgical resection is only rarely indicated. However, in selected cases long-term survival can be obtained after complete resection which remains a major prognostic factor.

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Stage Specific Treatment: Oncology

Erica Beaumont

Oncological Treatments can be used at any stage of the disease process providing the patient is fit enough.

Neoadjuvant treatment is used to downstage a tumour and eradicate systemic micrometastases. There is no routine role for neoadjuvant chemotherapy (1) or radiotherapy in NSCLC, but they can be used in Pancoast tumours. Radiotherapy is used in this setting in thymomas.

Adjuvant Chemotherapy is used for Stage 2 and above patients (2), but is more controversial in Stage 1B. Adjuvant radiotherapy has been shown to have a detrimental effect on survival (3) and so is only used if there are positive margins in NSCLC. It is also used for thymomas with a high risk of recurrence.

Radical radiotherapy alone is used for T1/small T2 tumours, where surgery is not possible. We prefer the FEV1 to be above 1L, but accept up to 0.8L depending on tumour position. Side effects include: tiredness, oesophagitis, pneumonitis, long term spinal cord damage and cardiotoxicity. Planning is done to maximise the dose to the tumour and minimise the dose to the normal tissue, keeping well below the tolerances of the major organs at risk. The main challenge in radiotherapy to the lung is to take tumour movement into account, newer ways of delivering radiotherapy include planning over using a 4D scan. Stereotactic radiotherapy delivers a higher dose per fraction in a smaller number of fractions and can be used when patients have a poorer PS or FEV1.

Chemotherapy and radiotherapy are used together for Stage II, IIIA and selected IIIB patients. Sequential treatment gives 4 cycles chemotherapy first and then radiotherapy. This is better than RT alone (4) but increases toxicity. Concurrent chemoradiotherapy again improves survival (5) but increases toxicity.

Palliative treatment is given for Stage IIIB and IV. If the patient is fit, chemotherapy is an option (precise drugs depend on histology). Radiotherapy can be used for symptomatic relief of local

symptoms (haemoptysis, cough, pain, SOB due to lobar collapse) and for brain and bone metastases.

Limited stage small cell cancer is treated with a combination of chemotherapy and radiotherapy. This can be either sequential or concurrent (6) depending on patient fitness. Prophylactic Cranial Irradiation is also used (7) and can be used in extensive stage disease that responds well (8). Extensive stage small cell is treated palliatively with chemotherapy. Small cell lung cancer is more responsive to treatment than NSCLC.

Mesothelioma is primarily treated with chemotherapy, but radiotherapy is used for port / drain sites to prevent seeding along the tracts.

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Neo-adjuvant and adjuvant therapy for NSCLC

Additional therapy to help improve survival rates may be delivered by

1. DXT
2. Chemotherapy
3. ChemoDXT

These forms of therapy may be offered either as

- Induction or neo-adjuvant - Prior to surgical intervention
- Adjuvant - After surgical intervention

Neo-adjuvant DXT

The randomised trials of pre-operative DXT are old (conducted in the 1960s). They included cobalt based technology and included a significant number of patients with T4 and N2/3 disease as well as a number of patients with small cell lung cancer. These trials demonstrated a reduced survival associated with pre-operative DXT and no improvement in local control. Of interest, a small (33 patient) trial of DXT published in 1984 in early NSCLC demonstrated a non-significant improvement in patients assigned to DXT as opposed to the surgery alone group (58% vs. 43%). Thus, there is currently no data to support the use of pre-operative DXT.

Neo-adjuvant chemotherapy

The majority of patients enrolled in trials of pre-operative chemotherapy are stage IIIa (discussed in more detail later). There is currently little evidence to support the use of neo-adjuvant chemotherapy in stage I/II NSCLC.

Adjuvant DXT

There is currently little data to support the use of adjuvant radiotherapy from a number of randomised trials as well as the PORT meta-analysis. These studies have not demonstrated a benefit and the PORT meta-analysis demonstrated a survival disadvantage for adjuvant DXT. However, these results need to be interpreted with the caveat that a large number of trials in the PORT meta-analysis used cobalt based technology as opposed to the current modern day standards. When these data are separated out into historical vs. modern day studies, the

survival disadvantage was clear in the cobalt group and a non-significant trend towards improved survival was seen in the modern day group.

Currently, for fully resected NSCLC there is no role for post-operative DXT.

Adjuvant chemotherapy for NSCLC

Following formal anatomical resection for NSCLC, recurrence is more likely to occur systemically rather than locally. Even if recurrences do occur locally, patients do not tend to die from it. For this reason systemic therapy is recommended.

Of the RCTs performed so far, there are a number of limitations. Few of the trial are stage specific and most group together stages I-III. The early trials used (compared to modern day practice) ineffective and potentially detrimental regimens. A number of trials failed to deliver the full course of chemotherapy initially planned.

A meta-analysis performed in 1995 demonstrated a 13% reduction (not statistically significant) in the risk of death for patients undergoing adjuvant chemotherapy following surgical resection. The lung adjuvant cisplatin evaluation (LACE) pooled data from the five largest trials completed since 2004 and demonstrated a 5% overall and 6% DFS for patients with stages II and III disease.

The IALCT published in 2004 was a multi-centre RCT of adjuvant chemotherapy following surgical resection vs. no additional treatment. Prior to initiation of the study, the individual centres had to decide which stages would be included, the dose of cisplatin per cycle and the other chemotherapeutic agent to be combined with cisplatin. The use of post-operative DXT was also centre specific.

To be eligible to be recruited patients were 18-75 years of age, had to have undergone complete surgical resection with no prior chemoDXT, with stage I-III and the ability to tolerate post-operative chemotherapy. The primary endpoint of this study was overall survival post-randomisation and secondary endpoints included disease free survival (DFS), secondary primary cancers and adverse effects. It was designed to detect a 5% improvement in survival at 5 years (required 3300 patients). Only managed to recruit 1867 patients (148 centres in 33

countries). Of the patients recruited ~1/3 were stage I and ~40% were stage III, which included ~25% of patients with N2 disease. Just over 1/3 of patients had a pneumonectomy performed. Post-operative DXT was administered to ~30% and of these 2/3 had N2 disease. Chemotherapy was incomplete in ~1/4 and this was mainly due to adverse effects

However, despite these issues, a statistically significant difference in the overall survival at 2 years 70.3% vs. 66.7% and at 5 years 44.5% vs. 40.5% as well as DFS at 2 years 61.0% vs. 55.5% and 39.4% vs. 34.3% for chemo vs. no chemo groups respectively was demonstrated. This evidence supports the use of 3-4 cycles of platinum based chemotherapy post-complete surgical resection and the benefit is the same as is seen in other solid organ cancers.

CALGB 9633

The meta-analyses for adjuvant chemotherapy post-complete surgical resection suggest that the benefit is greatest for those with stage II/III disease. The CALGB 9633 trial was designed to specifically investigate the role of adjuvant chemotherapy in stage Ib disease following complete resection. Aimed to randomise 500 patients and powered to detect a 13% improvement in survival. Due to slow recruitment only 384 randomised and analysis changed from two-sided to one-sided p-value. No significant difference in overall 5 year survival or DFS. However, for those patients with a tumour size > 4cm an improvement in overall survival and DFS was noted. Therefore the trial concluded that chemotherapy may be considered for patients with stage Ib and tumour size > 4cm.

Neo-adjuvant therapy for N2 disease

EORTC

This was an RCT of resection vs. DXT after a response to induction chemotherapy. Patients with histologically or cytologically proven N2 disease underwent induction platinum based chemotherapy. Patients were assessed for response (complete, partial or minor) – overall response rate 61%, prior to randomisation. Of 582 patients registered into the trial, 250 were excluded (mainly due to disease progression, stability or death). Leaving 332 patients randomised. There was no difference in either median survival or of progression free survival between groups and 5 year survival rates were 14% and 15.7% for DXT vs. surgery groups.

Several exploratory analyses noted sub-groups in the surgical arm with favourable characteristics including bilobectomy vs. pneumonectomy, pathological mediastinal response, complete vs. incomplete resection and avoidance of post-operative DXT.

Intergroup 0139

Patients with pathologically proven N2 disease were randomised to chemoDXT (interval assessment for disease progression), followed by either surgical resection or definitive DXT, with two additional cycles of chemotherapy administered in both groups. Of 429 patients randomised, 396 were eligible for analysis. A total of 155 patients underwent surgical resection (54 pneumonectomies). No difference was detected in either overall survival between groups, however, an improvement in DFS was seen for the surgical arm. Patients with a pathological response had increased survival compared with non-pathological responders and those with disease progression following interval assessment not undergoing surgery. In subgroup analysis, patients who underwent lobectomy had improved survival and those who underwent pneumonectomy did not.

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Selection for surgery - What's new?

Babu Naidu

Risk models may aid in making the decision for surgery and allow the surgeons to provide accurate information and obtain informed consent. The new BTS guidelines have incorporated Thoracoscore (Thoracic Surgery Scoring System) into the selection for surgery for lung cancer.

Thoracoscore is calculated based on the formula [(% prediction of death = Logit = -7.3737 + Sum (beta), Predicted death Rate $=e^{(Logit)} / (1 + e^{(Logit)})$] where beta (β) is constant based on 9 tested factors (age, sex, dyspnea score, American Society of Anesthesiologists score, performance status classification, priority of surgery, diagnosis group, procedure class, and comorbid disease)

Developed by Falcoz and colleagues it is a model with good accuracy to predict in-hospital and midterm mortality after general thoracic surgery. It was developed and evaluated in patients after all types of thoracic surgical procedures including oesophageal, pleural, and mediastinal surgery, after elective and urgent surgery, benign and malignant, and of all functional states. The new BTS guidelines have incorporated Thoracoscore into the selection for surgery for lung cancer. Its applicability in this fairly fit select group is uncertain. To give 2 examples

1.the division of risk of procedure into two categories i.e. pneumonectomy and other thus bundles together diverse procedures which are bound to exert different risk. Minimally invasive keyhole procedure removing <1 % of lung function will not carry the same risk as a bilobectomy open surgery removing one third of overall lung function.

2. the number of patients with poor performance status and/or breathlessness who would be selected for elective lung resection are very small but these are important factors defining risk in original cohort.

The ESOS (European Societies Objective Scores) is another model developed to identify preoperative risk factors associated with mortality after lung resection surgery based on the Formula $logit_2 = —5.8858 + (0.0501 * age) — (0.0218 * ppoFEV1\ \%)$

83 % of cases in the original study had cancer. The score is defined by age and post operative predictive FEV_1. Interestingly this latter factor was not a significant independent risk factor on multivariate analysis but the authors chose to use this measure as it could be defined clearly. Indeed the subjective score they also developed at the time which included age, type of procedure, ASA and dyspnoea score was liable to a degree of gaming hence the development of an objective score. Of note it is difficult to define how well the objective model performed in the defining cohort because no hard statistical data is presented on this in the original publication.

It will be important to validate these scoring systems in UK practice. Regardless, the issue of value to the patient of such defined mortality figures is questionable. Defined values might be of use in research and outcome assessment but quoting a range of risk to a patient might be more appropriate and easier to comprehend.

Perhaps of more relevance to a patient is the length of hospital stay and development of more common complications, neither the Thoracoscore nor ESOS can predict this. In summary these novel scoring systems are an important development in risk stratified outcomes assessment in thoracic surgery but their clinical value is yet to be defined in lung cancer surgery.

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Radical management of patients with lung cancer

In 2010, the BTS and SCTS updated the previously published guidelines on radical management of patients with lung cancer. A full review of these guidelines is not within the remit of this article, there are however, some pertinent points from the guidelines.

Currently lung cancer resection rates are variable between regions in the UK, between 5% to >25% and lung cancer survival is amongst the lowest in Europe.

There are several important definitions in the guidelines

Radical treatment – this implies a treatment that is given to improve survival significantly or has a curative intent e.g. surgery

Palliative treatment – this is treatment to improve quality of life which may or may not improve survival

Resectablity – a lesion is resectable if it can be completely surgically excised with pathologically clear margins

Operability – this refers to the ability of a patient to tolerate the procedure e.g. a lesion may be resectable but not operable due to the co-morbid state of the patient and the patient may be operable but not resectable due to the advanced nature of the disease.

Selecting patients for radical treatment

Patients due to undergo radical treatment should have as much information with regard to imaging to allow accurate staging of the disease process and histology to confirm diagnosis prior to delivering treatment.

Imaging

Any historical images should be made available to an MDT. CXR is not required for staging and diagnosis but forms part of the routine work-up of a patient. Contrast enhanced CT from the lower neck (level of vocal cords) to upper abdomen (unless history of previous abdominal malignancy) should be performed in all patients. Abnormal lymph nodes are >10mm in SAD and should be further assessed by PET.

All patients being considered for radical treatment (i.e. surgery) should undergo PET-CT to allow for accurate staging, in particular for occult metastatic disease and mediastinal lymph node staging. For PET +ve lymph nodes, histological diagnosis should be sought EBUS/mediastinoscopy/mediastinotomy to confirm or refute the presence of N2 disease. Presence of metastatic disease should also be confirmed histologically.

Other imaging modalities include USS for chest wall involvement and hepatic metastases, bone scan if PET is to be avoided, MRI to assess superior sulcus tumours and CT?MRI brain if the question of cerebral metastases is raised by the clinical condition of the patient.

Staging

In order to accurately stage patients, the 7th TNM classification should be used.

The 7th edition of TNM has made use of the largest database ever collected with wide geographical representation and including patients treated by all the modalities of care. There has been extensive analysis with both internal and external validation of all changes to the TNM classification. Changes to the TNM descriptors and stage groupings were derived strictly from the outcome measure of overall survival. The changes to the staging system for lung cancer with have implications for established treatment algorithms.

The T descriptor

Data was analysed and running log-rank statistics used to produce cut-points which corresponded to changes in survival at 5 years.

T1 was therefore split by size into T1a ≤2cm and T1b>2 ≤3cm.

T2 tumours were split into T2a >3cm≤ 5cm, T2b >5cm ≤ 7cm.

Tumours greater than 7cm (previously staged as T2) were upstaged to T3.

Regarding addition tumour nodule within the same lobe (previously pT4) analysis of the database showed these to have the same survival rate as T3 tumours and they were therefore reclassified as T3 tumours.

Regarding same-side additional nodules (previously pM1) these have a survival similar to other T4 tumours and were therefore reclassified as T4.

Pleural dissemination (previously classified as T4) had a much worse survival than other T4 tumours and was reclassified as M1a.

The N descriptor

No changes were made to the N descriptors.

A nodal map was developed to resolve the differences in nomenclature between Naruke's and Mountain-Dresler's maps.

Although not incorporated into the new TNM staging it was suggested that lymph node stations be classified by 'nodal zones i.e. upper zone (stations 1-4), aortopulmonary zone (stations 5 and 6), subcarinal zone, lower zone (stations 8 and 9), hilar zone (stations 10 and 11) and peripheral zones (stations 12 – 14). Although not incorporated into TNM7 the IASLC has introduced the concept of using nodal zones to subdivide the N component according to the extent of involvement of regional lymph nodes. They proposed subdivisions of N1a (single-zone N1), N1b (multiple-zone N1), N2a (single-zone N2), and N2b (multiple-zone N2). This needs further validation and will not be part of the new TNM changes.

The M descriptors

Due to clear differences in survival the M1 component has been divided into M1a and M1b. M1a is restricted to intrathoracic metastasis (including pleural dissemination and pleural effusion) and M1b if extrathoracic/distant metastases are present.

Changes to the TNM stage for lung cancer

6th edition	**7th edition**	**N0**	**N1**	**N2**	**N3**
T and M descriptors					
T1 (≤2cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2 cm ≤3 cm)	T1b	IA	IIA	IIIA	IIIB

T2 (>3 cm ≤5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (>5 cm ≤7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 (direct invasion)		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 (extension)	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral nodules)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral nodules)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Stages in bold are those that have changed in the 7th TNM classification

Risks associated with surgery

In order to accurately assess the risk of surgery for patients undergoing lung resection, 3 risks should be considered

1. Risk of peri-operative myocardial event
2. Mortality
3. Post-operative dyspnoea

Assessing peri-operative myocardial events

The ACC/AHA has published guidelines on assessing the peri-operative cardiovascular risk of patients undergoing non-cardiac surgery. Prior to proceeding with thoracic surgery, the following conditions require prior evaluation/treatment; unstable/sever angina or acute MI (within 7-30 days), decompensated heart failure, uncontrolled arrhythmias/high degree heart block and severe valvular heart disease. If none of these apply then the next step is a functional assessment. If the patient is able to perform activities equivalent to >4 METs without symptoms e.g. stair/hill climbing, heavy house work (lifting etc), moderate physical activity then surgery

should proceed. If it is not possible to assess the patient accurately then consideration of cardiac risk factors should be performed next, if patients have no risk factors then the risk of major cardiac complication is 0.4%, 1risk factor – 1%, 2 risk factors – 7% and >3 risk factors – 11%.

Risk factors include

- Thoracic surgery
- Ischaemic heart disease
- Prior or compensated cardiac failure
- Cerebrovascular disease
- Insulin dependent diabetes mellitus
- Pre-operative serum creatinine > 177

In summary, high risk patients with active unstable cardiac disease require further cardiological assessment/management. Those patients with good functional capacity and <2 risk factors can proceed to surgery. Patients with poor functional capacity and > 3risk factors require further investigation/cardiology work-up.

Assessing operative mortality

The 30-day mortality for lung resection in the UK is 2.3% for lobectomy and 5.8% for pneumonectomy respectively.

The Thoracoscore is a validated multivariable model for risk of in-hospital death amongst adult patients undergoing general thoracic surgery. It uses nine variables. The nine factors which the authors found to be significantly associated with the occurrence of in-hospital death were age, sex, dyspnoea score, ASA grade, performance status, priority of surgery, diagnostic group, procedure class and a composite comorbid disease score. The recent BTS and SCTS guidelines regarding radical management of patients with lung cancer suggest the use of a global risk score such as Thoracoscore for estimating the risk of death when evaluating and consenting patients for surgery.

Assessment of pulmonary function

Pre-operative PFTs should be performed to assess patient morbidity following surgery. The current guidelines recommend performing both FEV1 and TLCO as these do not correlate well with each other. FEV1 is a reasonable predictor of post-operative morbidity and TLCO a better predictor of mortality. In general predicted post-operative FEV1/TLCO should be > 40% with the caveat that mortality rates have been demonstrated to be acceptable with lower limits but this needs to be weighed against the risk of post-operative dyspnoea and those risks fully discussed with the patient.

There are a number of exercise tests that are available to help further with functional assessment of patients. Stair climbing has been described as a functional assessment tool, but the number of stairs/height climbed needs to be taken into account. In general ability to climb 5 flights indicates suitability for pneumonectomy and 3flights for lobectomy. Incremental shuttle walk testing can also be used. Patients able to manage >400m require no further assessment and those managing less than 25 shuttles require further assessment. Formal CPET can be performed with a treadmill or cycle ergometer. A V02max of >15ml/kg/min is the cut-off for good function.

In summary, patients with a ppoFEV1 and ppoTLCO> 40% require no further functional assessment. For those patients for whom one of these values falls below this parameter then further testing is recommended, if this functional assessment of good, then patients should be informed of the risk of mild-moderate post-op dyspnoea, if the functional assessments indicate moderate or poor functional assessment then patients need to be informed of the high-risk of post-op dyspnoea/O2 therapy. A caveat to this is the group of patient with predominantly upper lobe emphysema who may well benefit from an LVRS effect of lobectomy.

Lymph node management

In order to increase the accuracy of staging systematic lymph node sampling should be performed in patients undergoing resection for lung cancer. The current BTS guidelines suggest that at least 6 stations should be sampled of which 3 should be mediastinal.

Systematic sampling versus lymphadenectomy

There has been debate about how best to deal with mediastinal lymph nodes for many years and a large number of studies published regarding the subject. Despite many recommendations and guidelines suggesting that mediastinal lymph node dissection (MLND or lymphadenectomy) should be the standard of care for patients undergoing NSCLC resection when we look at real world data we find that many patients do not have mediastinal nodes sampled. This is well demonstrated in data from the STS database, which for 9033 cases showed only 65% had mediastinal node assessment of some type, 41% were reported as having nodal dissection, 12.4% nodal sampling and 8% nodal biopsy. This means that 35% of patients had no mediastinal nodes assessed. This figure is similar to that shown in a previous study by Little et al in which 42% of patients had no mediastinal nodes assessed. Therefore we know that there is disparity between the gold standard of care and real world practice with respect to mediastinal node assessment at operation. One of the first RCTs on the subject was from Izbicki et al in 1998. This trial showed no difference in long term survival between their sampling or lymphadenectomy groups with increased operative time, air leak and blood transfusion in the lymphadenectomy group. There was however a trend towards increased survival in patients with N1 or limited N2 disease in the lymphadenectomy group. Wu et al in 2002 demonstrated a survival benefit in the lymphadenectomy group, they found that median survival was 59 months in this group vs. 34 months in the sampling group; it was also shown that it was the stage IIIA patients who appeared to derive the most survival benefit from mediastinal lymphadenectomy. Keller et al in a non-randomised prospective trial of 186 patients undergoing MLND vs. 187 undergoing MLNS demonstrated improved survival with MLND vs. MLNS (57.5 vs. 29.2 months respectively), however, no difference in recurrence rates was found and the study included no morbidity or complications data. It is interesting to note that recently there have been studies looking at the impact or role of lymphadenectomy in the elderly patient as with an aging population this is an important consideration. Okami et al in 2009 found that mediastinal lymphadenectomy was a risk factor for post operative complications in patients over 80 undergoing lung resection for stage I lung cancers. Furthermore another study by Okasaka et al

in 2010 [i] showed there was no survival benefit for lymphadenectomy vs. lymph node sampling in patients over 70 undergoing lung cancer resection.

There has now been a much larger randomised control trial that any of the previous studies this was the American College of Surgery Oncology Group Z0030 Trial. This trial was designed specifically to evaluate whether MLND improves overall survival compared to MLNS in patients undergoing pulmonary resection for N0 or non-hilar N1, T1 or T2 NSCLC. This was a multicentre prospective randomised control trial. After final eligibility review, 1,023 patients were classified as eligible 498 in the MLNS group and 525 MLND group. Patients underwent sampling of 2R, 4R, 7 and 10R nodes for right sided tumours and 5, 6, 7 and 10L nodes for left sided tumours, these were sent for frozen section if any of these were positive they were excluded from the study however if these lymph node stations were negative for malignancy, patients were randomized to no further lymph node resection (MLNS) or complete MLND. The preliminary results of this study had shown no difference in overall rate of complications or mortality between the 2 groups. The final results of this study were presented at the 90th Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, May 1–5, 2010 and published in 2011. At final analysis it was found that there was no difference in survival between the two groups with median survival of 8.1 years with MLNS versus 8.5 years with MLND (p=0.25). There were also no differences shown in rates of local, regional or distant recurrence between the 2 groups.

Though this study showed no difference in survival or recurrence rates when comparing MLND with MLNS it is important to recognise that all of the patients in the study had undergone a thorough pre-resection nodal sampling with frozen sections of these nodal stations being evaluated. This type of thorough sampling is not practised in the majority of thoracic surgery centres and it is important to note that the results of this study should not be generalised to patients who have not had such pre-resection sampling. In fact the authors themselves concluded that, despite the results they had demonstrated, MLND should still the technique employed for all patients with resectable NSCLC as there was no increase in morbidity or mortality with this technique vs. MLNS.

VATS lobectomy

The Cancer and Leukaemia Group B (CALGB) 39802 study was designed to evaluate the technical feasibility and safety of VATS lobectomy as a treatment of early non-small cell lung cancer (NSCLC). This was a prospective multi-institutional study and aimed to standardise the definition of a VATS lobectomy as a procedure incorporating a traditional hilar dissection of structures, no rib spreading and using videoscopic guidance. There were also criteria as to the maximum length of the access incision, nodal dissection or sampling and removal of the specimen. There were 111 patients who had T1N0 NSCLC, 96 of these (86.5%) underwent successful VATS lobectomy. Median procedure length was 130 minutes with median chest tube duration of 3 days. Peri-operative mortality was 2.7%, complication rates were also found to be lower than those reported for lobectomy via thoracotomy. This study therefore demonstrated the safety of VATS lobectomy as well as helping to develop a more standardised description of the procedure.

Meta-analysis of the outcomes following VATS lobectomy

In 2008, Whitson et al published a systematic review of the literature on VATS vs. open lobectomy. In 2008 the CALGB [Cancer and Leukemia Group B] 39802 study had previously demonstrated the feasibility of thoracoscopic lobectomy and suggested advantages in quality of life outcomes. Plans for a randomised control trial or a registry trial had failed to achieve funding and therefore this study by Whitson et al a meta-analysis of the available literature was carried out in order to further evaluate VATS vs. open lobectomy. A total of 38 articles were included in the final analysis with 22 providing data on VATS and 27 on thoracotomy. In total the studies involved 3256 thoracotomy and 3114 VATS lobectomy patients. The overall complication rate in the VATS patients were significantly lower than in thoracotomy patients ($p=0.018$, 16.4% vs. 31.2% respectively). VATS lobectomy also demonstrated statistically significant decreases in chest tube duration and length of stay. When overall annual survival rates were examined it was found VATS lobectomy showed an absolute survival advantage ranging from 5% at 1 year up to 17% at 4 years ($p=0.003$).

This study has several limitations not least of which is the fact that it is essentially an observational study as only one of the studies it includes was a randomized study. There is also potential bias in the VATS studies included as surgeons are less likely to have published data if there outcomes with VATS were inferior to open thoracotomy.

Pulmonary function as a predictor of outcome following lobectomy

It has been suggested that patients with poor pulmonary function tolerate VATS lobectomy better than a standard open procedure. In a retrospective study evaluating patients undergoing lobectomy for primary lung cancer with a preoperative forced expiratory volume in 1 second (FEV1) or diffusion capacity to carbon monoxide (DLCO) of less than 60% predicted. There were 340 patients who met the above criteria 173 underwent VATS lobectomy and 167 open lobectomy. Overall operative mortality was 5%; DLCO, FEV1 and thoracotomy as the surgical approach were all found to be significant predictors of pulmonary complications by multivariable analysis. However when patients were analysed by operative approach it was found that for VATS lobectomy patients DLCO and FEV1 were no longer significant predictors of pulmonary morbidity, though they were for patients undergoing thoracotomy. This suggests that VATS should be the preferred surgical approach for lobectomy in patients with poor PFTS due to the decreased morbidity associated with a minimally invasive approach.

Health economics of VATS lobectomy

Walker et al designed a study to address the cost effectiveness of VATS vs. open lobectomy as there are often concerns raised about the cost of stapling devices used in VATS procedures. The study population was made up of 346 patients undergoing lobectomy 93 via VATS and 253 via thoracotomy. Though it was found that theatre costs were higher for VATS lobectomy vs. thoracotomy there was a decreased cost in the VATS group for HDU care and hospital stay. This translated into an overall decrease in the cost of a VATS lobectomy (8023 +/- 565 Euros) compared with an open lobectomy (8178 +/- 167 Euros) ($p = 0.0002$). VATS bilobectomy was slightly more expensive than an open one but this difference was not statistically significant.

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Locally Advanced Lung Cancer

Philippe G. Dartevelle

Background

To assess operative mortality, morbidity, and long-term results of patients with surgically resected T4 non-small cell lung carcinoma (NSCLC).

Methods

A retrospective review of 271 patients with T4 NSCLC between 1981-2006 was undertaken. They were divided into four subgroups: 126 patients with superior sulcus tumors, 92 with carinal involvement, 39 with superior vena cava replacement and 14 with the tumor invading other mediastinal structures. There were 221 men and 50 women with a mean age of 56.3 years. Resection was complete in 249 (92%) patients. The pathologic N status was N0/N1 in 208, N2/N3/M1 in 63 patients.

Results

Operative mortality and morbidity rates were 4% and 35%, respectively. Overall 5-year survival rate was 38.4%. It was 36.6% for superior sulcus tumor, 42.5% for carinal involvement, 29.4% for SVC replacement, and 61.2% for mediastinal group. By multivariate analysis, only three factors influenced survival: nodal status (N0/N1 vs. N2/3/M1; 43% vs. 17.7% at 5 years, respectively; p=0.01), complete resection (R0 vs. R1; 40.4% vs. 15,9%, respectively; p=0.006), and invasion of the subclavian artery (with vs. without invasion; 24.9% vs. 41.7%, respectively, p=0.02).

Conclusions

In highly qualified centers, radical surgery of T4 N0/N1 NSCLC can be performed with a 4% mortality rate and may yield a 43% five year survival rate. These results seem to indicate primary surgery as the treatment of choice for T4 NSCLC, whenever a complete resection is thought to be technically feasible and patient's condition compatible with the extent of the planned surgery.

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Management of airway obstruction

Maninder Kalkat

A wide variety of benign and malignant conditions can result in anatomic or functional narrowing of the trachea. The most effective and ideal treatment for almost all benign and few malignant conditions is surgical. Using mobilization techniques, approximately half of the adult trachea can be resected and reconstructed by primary anastomosis. Post intubation tracheal stenosis remains most common indication for tracheal resection and reconstruction. Resection rates approaching 50 – 75% have been reported for rare primary tracheal tumours.

However a large number of patients with symptomatic and life threatening airway pathology are not candidates for definitive surgical correction because of the extent of the disease or comorbidity. Patients with severe central airway obstruction from malignant causes have disabling symptoms of dyspnea, respiratory distress, and obstructive pneumonia. For many of these patients, in the absence of intervention, the airway pathology may be the direct cause of distressing death from suffocation. The endoscopic techniques are minimally invasive and can provide significant palliation. Although the long-term outlook in these cases is often dismal, the temporary or permanent relief of airway obstruction provides significant palliation with improvement in quality of life and, in few cases increase in survival.

The malignant causes of airway obstruction include direct extension from adjacent tumour – bronchogenic (30 -50%), oesophageal or thyroid, or metastasis from renal, breast or thyroid tumours. Primary tumours of central airways are rare. Extrinsic compression from hilar, mediastinal tumours or bulky lymphadenopathy counts for rest of the causes.

The management of these patients is individualized depending on the underlying cause.

Endoluminal lesions are managed by coreout of tumour, thermal laser vaporization, photodynamic therapy, brachytherapy, cryotherapy, and electrocautery. However, these therapeutic bronchoscopic techniques provide transient benefit and have to be consolidated with either chemotherapy or radiotherapy.

Airway stents are a valuable adjunct to these techniques and can provide prolonged palliation from rapidly recurrent endoluminal tumour, extrinsically compressing mass or managing trachea-oesophageal fistulae. An ideal stent should be easy to insert or remove, have sufficient strength, flexible to mimic natural airway, promotes clearance of secretions, biologically inert and does not migrate. None of the various stents available (metallic, non-metallic, covered, uncovered) satisfies all these conditions. The silicone stents are inexpensive, less reactive with minimal granulation, solid and hence no tissue ingrowth and can be repositioned and removed easily. However, these are difficult to insert, have reduced inner diameter and can migrate. The metal stents on the other hand are easy to insert, larger internal:external diameter ratio, conforms to distortions and curves and gets incorporated into airway helping in mucociliary clearance. The disadvantages include difficulty in removal and uncontrolled expansion and erosion into adjacent structures.

Any attempt to manage central airway obstruction should involve team approach involving experienced anaesthetist, surgeon, nursing staff and physiotherapist for optimal results and avoidance of complications.

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Endobronchial therapies

Therapies for endobronchial disease are most commonly delivered in a palliative setting for malignant disease; however, they can be required in the setting of benign disease. The most common therapies used are usually delivered via the rigid bronchoscope and include laser, photodynamic therapy (PDT) and stent placement. Patients who gain most from these procedures are those with localised airway obstruction and viable distal lung.

Laser

The most commonly used laser in thoracic surgery is the Nd: YAG, it is possible to deliver it via a flexible bronchoscope and its most common indication is in the palliation of inoperable major airway tumours to relieve symptoms. It has excellent performance in treatment of proximal (trachea/main bronchi) lesions compared with more distal lesions

There are 10 rules of laser

1. Know the surrounding anatomy and danger zones e.g. aortic arch
2. Have a laser team, surgeon, anaesthetists, ODA, nurses familiar with the procedure and the equipment required
3. Any endoluminal growth may be lasered, but purely extrinsic compression is a contra-indication.
4. Use a rigid bronchoscope with two suction catheters in high grade obstruction
5. Careful monitoring, in the event of hypoxaemia interrupt treatment long enough to treat the patient. Intubate if necessary
6. Fire the laser parallel to the wall, never directly at it
7. Coagulate using the laser, but mechanical resection after laser is preferable to laser resection alone
8. Control haemorrhage, even slow bleeding causes hypoxaemia if left unattended
9. End each procedure with a thorough bronchial toilet
10. Observe and monitor the patient in the recovery for a reasonable period of time

Complications can occur and with experience can be < 4% with a mortality < 1%

Photodynamic therapy

PDT allows for selective destruction of tumour whilst surrounding normal tissue is preserved. This is achieved by administration of a photosensitising compound (UK most commonly Photofrin, intravenously). This is administered 48 hours prior to the procedure; it accumulates in all cells, but with greater concentrations in malignant tissue. As it photosensitises all tissues, patients must take appropriate measures to protect themselves from light exposure. At bronchoscopy a diffuser fibre is placed alongside the area to be treated and illuminated, this leads to formation of reactive oxygen species with subsequent tissue destruction. Depth of penetration is ~5mm. Toilet bronchoscopy should be performed at 48-72 hours and a further may be required after another 48-72 hours. Patients remain photosensitised for between four to eight weeks and must therefore avoid direct exposure to sunlight and bright light during this time period.

PDT is contra-indicated in patients with porphyria, allergic to porphyrin or in the setting of traceo-oesophageal fistula. The lifestyle limitations imposed by photosensistisation should be taken into account when considering patients for palliative PDT.

Stents

Stenting may be used to treat either benign or malignant disease processes. The main stent types are either silicone based or expandable metal.

In general the treatment of benign airway strictures is by resection and if stenting is required then a large number of these patients will require re-intervention.

Silicone based stents

These are straight or Y-shaped and can be manufactured for individual patients. They are made of silastic rubber and include Dumon (studded), Hood (flanged) and Polyflex (silicone mesh with outer polyester coating). Silicone stents are resistant to lateral compression andprevent ingrowth, they are easier to remove but due to this property may be complicated by migration. They eliminate mucociliary clearance and may be prone to mucus plugging. They are preferred in benign disease (with the caveat that they are second line therapy to reconstruction).

Expandable metal stents

These are constructed from a variety of materials including cobalt alloys (Wallstent), stainless steel (Gianturco) and nitinol (Ultraflex). They may be delivered either proximally, distally or from the centre of the stent. Proximal delivery is best suited for proximal strictures. They may also be partially covered with polyurethane or silicone (Ultraflex). They are easy to insert, adapt to irregular shaped strictures and although potentially removable can be extremely difficult to extirpate. Non-covered stents allow for tumour ingrowth and covered stents have been designed to prevent tumour ingrowth.

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SURGERY FOR MESOTHELIOMA

David Waller

The presentation will cover the following areas :

1. **Epidemiology**

   Why this problem is not going away. Who is at risk

2. **Selection criteria**

   The importance of cell type. The importance of nodal disease. Problems in current staging system. The differences from lung cancer staging.

3. **Surgical strategy**

   The best initial procedure. Surgical palliation. Surgery to prolong life. Treatment protocols.

4. **Surgical techniques**

   Extrapleural pneumonectomy. Pleurectomy/decortication. VATS pleurectomy/decortication. Management of surgical complications

5. **Multimodality treatment**

   Chemotherapy – neoadjuvant, intracavitary,adjuvant. Radiotherapy – radical hemithorax, prophylactic

6. **Clinical trials**

   MARS, MARS 2, MesoVATS

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Surgery in the Management of Malignant Mesothelioma

The majority of patients with malignant mesothelioma present with advanced disease, the median survival from diagnosis is between and 18 months. Poor performance status, advanced stage disease, sarcomatous histology (as compared to epithelial or mixed) and left sided pleural disease are all associated with poor prognosis. Most patients present with dyspnea due to the presence of a malignant pleural effusion and over half have chest wall pain at presentation. In the majority of patients the aim of surgery is diagnosis and palliation of symptoms, a small number of patients undergo radical surgery for local control.

Palliation of symptoms of breathlessness secondary to a malignant pleural effusion is achieved by draining the effusion and carrying out a form of pleurodesis to prevent re-accumulation, this is effective in the majority of patient. Talc pleurodesis is most commonly used and is successful in 80-95% of patients. An alternative is subtotal parietal pleurectomy which has the advantage of providing large tissue volumes for histology and like talc pleurodesis provides good symptom control with low morbidity in the majority of patients.

Patients with advanced pleural disease may present with a trapped lung where the lung is encased by a tumour cortex. In these cases where the lung fails to re-expand following drainage of the effusion neither chemical pleurodesis nor parietal pleurectomy will achieve palliation where pleural apposition cannot be achieved. Alternative therapies to palliate dyspnea in these patients include pleuroperitoneal shunts and long-term indwelling pleural drainage catheters but these techniques do not give any lung re-expansion in the trapped lung and have reported complication rates of 15-20% respectively. An alternative, but more aggressive treatment for the palliation of trapped lung is visceral pleural decortication where decortication is undertaken to the extent required to achieve pleural apposition. Martin-Ucar et al published their protocol and results of de-bulking surgery in the management of patients with trapped lung. There were no cases of recurrence of pleural effusion and good palliation of both dyspnea and pain was achieved at 6 weeks and 3 months. The 30 day mortality rate of 7.8 % is comparable to that of talc pleurodesis. Their results show that palliative decortication (VATS or open) has a role in selected patients presenting with advanced pleural disease.

Radical surgery for malignant mesothelioma is much more controversial and includes extra-pleural pneumonectomy (EPP) and radical decortication. The mesothelioma and radical surgery (MARS) trial was developed to test the feasibility of carrying out a randomised controlled trial (RCT) to investigate the role of EPP on survival. Patients were randomised to trimodality treatment (chemotherapy, EPP and radical hemi-thoracic radiotherapy) or identical chemotherapy and any non-surgical treatment thought appropriate. The trial used a two-stage consent process; in the first-stage eligible patients received three courses of chemotherapy. Prior to the second consent all patients were restaged and reviewed and if they remained eligible (i.e. had completed the chemotherapy course and had no evidence of disease progression) they were randomised to EPP and radiotherapy or any appropriate non-surgical therapy. Recruiting completed in 2008 with 50 patients out of the initial 112 being suitable for and having agreed to randomisation, thus demonstrating that randomisation of patients to surgery versus no surgery was possible (Treasure et al., 2009). The principle report of the MARS study was published in August 2011 (Treasure et al) and their conclusions were damming. They concluded that due to the high morbidity associated with EPP in this trial and other non-randomised studies that a further larger trial was not feasible. The data from the first MARS trial suggests that radical surgery in the form of EPP within tri-modality therapy offers no benefit and possibly harms patients.

Even before the results of the MARS trial there had already been a move away from EPP towards lung sparing surgery as a radical treatment of malignant mesothelioma. This has been prompted by the retrospective reporting of a number of large centres the results of which showed high rates of complications with EPP (up to 50-60%) (Sugarbaker, 2004; Schipper et al, 2008) with Schipper et al reporting a 3 year survival with EPP of only 14 %. At the same time groups had started to report improved or similar survival with radical pleurectomy/decortication versus EPP with a decreased morbidity. The combined results of 3 large centres in the USA were published in 2008 (Flores et al) reporting an improved survival with pleurectomy/decortication versus EPP. The Leicester group also in 2008 (Nakas et al) reported their results, having shifted their practice towards radical lung sparing surgery with no detriment to survival.

Although surgery has a clear role in diagnosis and palliation for malignant mesothelioma the exact part lung sparing surgery has to play in the radical management of these patients is still to be fully determined.

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Malignant Pleural Effusion

In health there is a constant production and absorption of pleural fluid governed by Starling's forces. Parietal pleura has a net production of fluid (hydrostatic pressure is greater than osmotic pressure) and pulmonary capillaries are responsible for absorbing 90% of fluid from the pleural space (hydrostatic pressure less than osmotic pressure). Mediastinal and diaphragmatic lymphatic take up around 10% of the pleural fluid. In malignant disease there is often a moderate rise in the protein content of the pleural fluid (normal is 10-20 g/l) either due to a failure of lymphatics to absorb or an increase in production/leak due to malignant involvement of the pleura. The increase in protein content further increases the tendency for pleural fluid production.

Light's criteria are used to distinguish exudates from transudates on the basis of protein content, glucose, pH, and LDH. Generally transudates (low protein) are associated with heart failure and hypoalbuminaemia. Exudates (high protein) are characteristic of infection. Most malignant effusions are intermediate in protein content and highly variable in other respects. The diagnosis of malignant pleural effusion is based on clinical context, cytology of the effusion and histology of the pleura.

The role of thoracic surgery in patients with malignant pleural effusions is in both the diagnosis and symptomatic relief for palliation.

Diagnosis of whether a pleural effusion is a manifestation of disseminated malignancy will affect the subsequent management of the effusion and the treatment of the patient. Cytology is diagnostic in just under 50% of patients and this yield may increase with repeated sampling. VATS has a high diagnostic yield allowing direct visualisation of the pleura and targeted sampling. In cases with no diagnosis pleural biopsy maybe the principle reason for surgery with pleurodesis for symptomatic control being a secondary aim of the procedure.

Symptomatic relief can be obtained by aspiration/drainage of fluid and subsequently maintained by obliterating the pleural space by pleurodesis. Even with malignant pleural effusions diagnosis may determine whether pleurodesis is required i.e. if the pleural fluid resolves as the underlying

disease responds to treatment (eg. chemotherapy for lymphoma) then pleuradhesis is not required. If however the effusion persists and recurs after drainage then pleurodesis warranted.

Pleurodesis is generally performed at the bedside by oncology and respiratory practitioners, and performed in theatre mainly by talc insufflation during video-assisted thoracoscopic surgery (VATS). Although talc is used by the vast majority of thoracic surgeons various other chemicals have been used mainly by physicians. These include anti-neoplastic agents, irritants and pro-inflammatory drugs. The results of two systematic reviews (Walker-Renard et al 1994, Tan 2006) and a Cochrane review (Shaw et al 2004) have shown that talc is the most effective and cheapest agent.

Published randomised controlled trials (RCT) comparing VATS with bedside pleurodesis (Evans et al 1993, Yim et al 1996 and Manes et al 2000) show only a marginal advantage of VATS. This of course does not account for the fact that in many surgical cases talc pleurodesis is a secondary benefit of VATS the primary goal often being diagnosis. In addition these studies excluded patients in whom the lung failed to re-expand following drainage of effusion and these are group of patients who are more likely to be successfully treated by surgery than bedside talc. In addition is likely that surgical talc pleurodesis will generally be performed under similar circumstances to that seen during a trial, the standard of bedside talc pleurodesis performed outside of a trail protocol is likely to be much more variable.

Other surgical techniques include pleurectomy (parietal alone or visceral), shunts or long-term drains. Visceral pleurectomy is a much more major undertaking and should be reserved for patients in whom pleurodesis is unlikely to control their symptoms such as patients with a trapped lung (the lung is tethered by a tumour or fibrin coat) and in whom their expected survival justifies the increased complications (such as prolonged air leak). Pleuroperitoneal shunts (Denver shunts) and long-term drains are a less invasive alternative to decortication which can be successfully used in trapped lung where simple pleurodesis is expected to fail. The reported complication for Denver shunts are of the order of 15% and for long-term drains is around 20%.

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Surgery for Pulmonary Infections: Tuberculosis, Lung Abscess, Aspergillosis and Bronchiectasis.

Juliet King

Surgery for pulmonary infections comprises a small but challenging proportion of the thoracic surgical workload. The majority of these patients are managed medically, but those that require surgery are often in poor health, with compromised immune function, and significant co-morbidities. The required surgery is technically challenging and associated with a high incidence of morbidity and mortality. There is little good quality clinical evidence to guide decision making in these conditions, and even large specialist centres have limited experience of managing patients in the current era. Surgery with therapeutic intent is generally reserved for failure of medical therapy and life-threatening complications.

Tuberculosis

Pulmonary TB is a major health issue with over 8 million new cases, and more than 1.5 million deaths a year world-wide. The incidence of TB in the UK had fallen dramatically in the last 150 years, but is now on the increase and the UK currently has the third highest incidence in Europe. Within the UK >70% of cases are in those born overseas, and there is a strong association with overcrowding, poor social circumstances and reduced immune function. Less than 1% of all TB cases require surgical intervention. The spectrum of surgery ranges from diagnostic procedures through to the management of destroyed lung, bronchopleural fistula (BPF) and life-threatening haemoptysis. The greatest challenge remains the management of an infected pleural space associated with destroyed lung and / or BPF.

Lung Abscess

Lung abscess is most commonly the result of aspirated infected oropharyngeal secretions, and associated with poor oral hygiene, sinusitis, and chronic reflux. Multiple abscesses may be a feature of infective endocarditis, i.v. drug abuse and impaired immune function. Pathogens reflect the cause, with most abscesses secondary to Klebsiella, Staphylococcus and anaerobes. The majority of cases respond to long term targeted antibiotic therapy, but persistent infections

and those associated with empyema, BPF or suspected cancer may require surgery. Sub-lobar resections are preferred if possible to minimise space problems post-operatively.

Aspergillosis

There are three distinct patterns of disease secondary to pulmonary colonisation with Aspergillus species. Invasive aspergillosis is associated with impaired immune function and is a life-threatening condition that is best managed medically with antifungals. Allergic aspergillosis is caused by an allergic reaction to the fungus which is normally managed with corticosteroids. Aspergilloma (mycetoma) refers to the development of a fungal ball, usually within abnormal lung e.g. TB cavity. Although the majority of these are asymptomatic surgical intervention is occasionally required for pleural involvement or massive haemoptysis.

Bronchiectasis

Bronchiectasis is defined as an irreversible dilation of proximal bronchi with associated chronic infection. This can occur as part of a congenital lung disease e.g. cystic fibrosis, but many cases are acquired following severe pulmonary infection or secondary to airways obstruction. Surgery is indicated for significant haemoptysis and in those with reduced quality of life secondary to chronic infections. Best surgical results are seen in those with cylindrical subtypes, absence of sinusitis and localised and resectable disease, in whom 80-90% will have some clinical benefit.

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Bullous Disease: Primary Pneumothorax

Mr. M. E. Cowen

Pneumothorax is air in the pleural space. Primary pneumothorax occurs in otherwise healthy patients without any lung disease with an incidence of up to 28/100,000 per year for males. There is a strong association with smoking and despite no underlying lung disease sub pleural blebs and bullae are likely to play a role and are present in 90% of patients at surgery and 80% of patients on CT scan,

It is not felt that physical activity causes a pneumothorax. Most cases are symptomatic but nearly half the patients wait more than 2 days with symptoms before seeking medical attention. Clinical history and physical examination usually suggest the presence of a pneumothorax but are not reliable indicators of pneumothorax size. Diagnosis is normally established by plain chest X-ray. Size of the pneumothorax is divided into “small” or “large” depending on the presence of a visible rim of <2cm or >2cm between the lung margin and the chest wall (2cm approximates to a 50% pneumothorax).

Patients with a small pneumothorax and minimal symptoms do not require hospital admission but are discharged with appropriate advice. Symptomatic patients who require admission require active intervention, observation alone is inappropriate. Supplemental high flow oxygen should be given. Simple aspiration is recommended as first line treatment for all primary pneumothoraces requiring intervention (A). If more than 2.5L aspirated or the procedure fails a second aspiration should now only be considered if there were technical difficulties and an intercostal drain should be inserted. Pneumothoraces which fail to respond within 24 hours should be referred to a respiratory physician(C). Chemical pleurodesis should not be considered after a first time uncomplicated primary pneumothorax. Chemical pleurodesis with tetracycline can be recommended for recurrent primary pneumothorax when surgery is not an option.

With the statistical and perceived risk of recurrence the accepted indications for surgery are:

Second ipsilateral pneumothorax

First complicated pneumothorax

Bilateral spontaneous pneumothorax

Persistent air leak

Spontaneous haemothorax

Professions at risk

Pregnancy

Surgical treatment is based on two principles, firstly resection of the cause of the air leak to remove the underlying defect and secondly create pleural symphysis.

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Management of Secondary Pneumothorax (PTX)

Richard D. Page

- Air in pleural space arising from diseased underlying lung (emphysema, bullae, ARDS, lung infections, malignancy etc)
- May lead to symptoms out of proportion to size of PTX on x-rays due to poor reserve and “tensioning” in association with pleural adhesions.
- CT scans essential to determine anatomy of PTX and assess underlying condition of lung
- Massive surgical emphysema a common association. Frightening for patient, relatives and hospital staff but rarely inherently dangerous. Treated by effective pleural drainage along with timely surgery as indicated by the underlying PTX
- Virtually always requires drainage as opposed to aspiration
- Surgical management individualised. Determined by condition and reserve of patient and prognosis of underlying condition affecting the lungs. More often dealt with non-surgically (i.e. with drainage alone), as compared to primary PTX. Avoid surgery on patients requiring positive pressure ventilation.
- Secondary PTX may be a pre-terminal development. In this situation palliation of the symptoms produced by the PTX is the priority, and it may not require specific treatment at all. “Treat the patient not the CXR or CT”

Surgical treatment of secondary PTX

1. Staple/suture the site of air leak. Consider buttressing of staple lines and the use of sealants. May usefully involve bullectomy and lung volume reduction surgery.
2. Pleural space obliteration
    a. Parietal pleurectomy
    b. Talc pleurodesis

c. Abrasive pleurodesis

3. VATS or open techniques?

    a. Individualised according to patient and surgical conditions

    b. Usually limited by pleural adhesions, especially after extended pleural drainage

    c. Essential to visualise and control putative air leak

    d. Open surgery more frequently indicated as compared with primary PTX

The Management of Spontaneous Pneumothorax

Pneumothoraces are classified as spontaneous or traumatic. Spontaneous pneumothoraces (SP) are further classified as primary or secondary. Primary spontaneous pneumothoraces (SPP) occur in otherwise healthy individuals due to the rupture of sub-pleural blebs and bullae found most commonly at the apices. The rest of the lung parenchyma being essentially normal. PSP occur in young adults (up to early 30's) and are more common in tall slim males. There is an increased incidence in smokers.

Secondary spontaneous pneumothoraces (SPP) are those occurring in a background of abnormal lung. The most common aetiology of SPP in the UK is chronic obstructive airways disease but they also occur in any lung disease that breaches the visceral pleura including TB, primary or secondary lung cancers, Wegener's granulomatosis, lymphangiolyomyomatosis (LAM), Langerhans histiocytosis and many more.

The management of pneumothoraces falls into immediate treatment, to evacuate air from the pleural space allowing re-expansion of the lung, and definitive treatment to prevent or reduce the risk of further recurrence. The British Thoracic Society (BTS) Guidelines deal with both the initial management of SP and subsequent therapies to reduce the risk of recurrence.

Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010.

MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group.

Thorax. 2010 Aug;65 Suppl 2:ii pp18-31.

Guidelines on management of spontaneous pneumothorax were previously published in 1993 and then again 2003.

Management of Acute Presentation:

In differentiating between spontaneous pneumothoraces that can be managed by observation alone and those requiring intervention the latest BTS guidelines stress the importance of clinical compromise and give less emphasis to the size of pneumothorax than in previous guidelines.

They recommend observation alone for small, closed, asymptomatic or mildly symptomatic pneumothoraces, the majority of which can be managed on an outpatient basis. Indications for active treatment are breathlessness and the need for supplemental oxygen, they emphasise that the need for active treatment is higher with SPP as their tolerance is less compared to the patient with normal lung function. Size is now only a relative indication, the cut-off between large and small being taken as over 2cm (approximately 50% pneumothorax), a large pneumothorax is taken as >2cm rim between lung at chest wall (measured at the level of the hilum), 2cm is a compromise between risk of needle trauma and increased time to resolution if untreated. .

In patients requiring active intervention they suggest that needle aspiration (NA) (14-16G needle) can be as effective as large bore (20Fr) tube drainage in the management of some patients. Needle aspiration failure rates however, have been reported as being up to 30% in some studies. They recommend stopping NA after 2.5 litres of air as if more than this is aspirated then there is probably a persistent air-leak and a formal chest drain required, the procedure should not be if the pneumothorax fails to resolve (unless there was a technical difficulty i.e. blockage or kinking and again a drain should then be inserted. The authors acknowledge that with the wide availability of Seldinger type drains practitioners may prefer to insert a small seldinger drain (8-12 Fr) rather than attempt NA.

Patients presenting with haemodynamic compromise, tension, bilateral or haemo-pneumothoraces should usually be treated by chest drain insertion. Patients in which NA fails (remain symptomatic or have residual space >2cm in PSP or >1cm in SPP) will require a chest drain. NA is acceptable as first line management in patients with PSP but in those with SPP ICD should be used as first line in symptomatic patients or in those with a pneumothorax of over 2cm.

Regarding the use of suction the BTS advises that suction is not routinely recommended as they suggest this increases the risk of re-inflation pulmonary oedema (Matsuura et al 1991).

Regarding the specific management of SPP all patient should be admitted for at least 24 hours

Supplemental oxygen should be given (as per BTS guidelines), not only does this improve hypoxaemia but has been found to increase by up to four times the rate of resolution of

pneumothoraces (Northfield 1971). Most will require insertion of a small bore chest drain. NA should only be attempted in patient who are not breathless and have pneumothoraces between 1 and 2 cm in size. In these patients an early CT scan maybe required to differentiate bullous disease from a pneumothorax. In SSP consider early ambulatory management with a one-way valve (Heimlich valve). If these patients have a persistent air-leak (>48 hours) they should be discussed with a thoracic surgeon.

Medical Pleurodesis

Ideally pleurodesis should be carried out surgically (VATS or open) as the procedure has a low morbidity and high success rate and allows both management of the underlying cause (bleb/ bullae) and pleural symphysis. However, if unfit for surgery (or the patient refuses surgery) consider medical chemical pleuradhesis. Scleroscents include tetracycline (good short term results but higher long-term recurrence rate), doxycycline, minocycline and most commonly used sterile talc.

Indications for Surgical Referral

Indications: Second ipsilateral pneumothorax

First contralateral pneumothorax

Synchronous bilateral SP

Persistent air-leak or failure of lung to re-expand (despite ICD) 3-5/7.

Spontaneous haemothorax, tension pneumothorax

Professionals at risk (pilots/divers)

Pregnancy

Pregnancy and PSP

There is an increased incidence of PSP during pregnancy and parturition. BTS guidelines advise observation only if the mother is not dyspnoeic, there is no foetal distress and the pneumothorax is small. If any of these are present needle aspiration should be used with insertion of an ICD if there is a persistent air-leak. There is an increased incidence of recurrence

with spontaneous delivery or caesarean section therefore elective assisted delivery at or near term with regional anaesthesia is advocated. Elective surgical management should be considered following delivery to decrease the risk in subsequent pregnancies.

Surgical Intervention for Spontaneous Pneumothorax

There is general consensus in the literature that the recurrence rate after one SP is around 30%, and after two is over 50%. Therefore most surgeons offer elective surgery following a second PSP. Surgery often allows the cause of the pneumothorax (bleb or bullae) to be removed in addition to creating a pleural symphasis. All surgical procedures for PSP reduce the recurrence rate to low single figures. To answer the question of whether VATS is comparable to open procedures in reducing recurrence a number of randomised controlled trials (RCT) have been carried out. Although no RCT has been sufficiently powered to answer the question of whether VATS has a higher recurrence rate than that of an open procedure the systematic review of both randomised and non-randomised trials published by Baker et al (2007) has demonstrated that VATS is associated with a four-fold increase in recurrence when a similar pleurodesis procedure is carried out compared to an open operation. It maybe that technical difficulties including the presence of a steeper learning curve for VATS versus open procedures exists. An additional factor maybe that the higher recurrence after VATS could be secondary to a decreased systemic inflammatory response with VATS versus open surgery (Walker et al 2007).

Open thoracotomy and pleurectomy remains the procedure with the lowest recurrence rate (approximately 1%). VATS with pleurectomy and abrasion has a recurrence rate of 4-5% but many studies have shown it to be better tolerated in terms of less post-operative pain, decreased post-operative stay and improved pulmonary gas exchange post-operatively. Sedrakyan et al (2004) demonstrated in their systematic review that VATS was associated with decreased pain, decreased limitation of physical activity and a decreased hospital stay. The prospective results of Ben-Nun et al (2006) showed a statistically significant reduction in post-operative analgesia requirements as well as a reduction in referral to the chronic pain team (13 referrals in the thoracotomy group and none in the VATS group).

Although VATS procedures for pneumothoraces do seem to be consistently associated with a modest increase in recurrence many surgeons would agree that this may be preferable to the possibility of higher complications in terms of pain and other morbidity associated with an open procedure especially when a repeat operation can be relatively easily undertaken if required (Treasure 2007).

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Emphysema

Destruction of the pulmonary parenchyma leads to loss of functional lung and a reduction in the surface available for gas exchange. With ongoing destruction of the lung tissue, there is progressive loss of elastic recoil and expansion of volume. This leads to the typical hyperfinflated chest with widening of the rib spaces and diaphragmatic flattening. The additional presence of bullous disease can lead to a pressure effect on the surrounding normal lung tissue further limiting respiratory function. Not only does the destruction of the lung tissue lead to a loss in the available surface for gas exchange but the anatomical changes that occur further increase the work of breathing and make respiration less efficient by placing the patient at a mechanical disadvantage.

Surgical management of emphysema involves bullectomy, lung transplantation and LVRS. All three of these procedures have a high morbidity and mortality. Therefore surgical management is reserved for those patients refractory to optimal medical therapy with a desire to undergo pulmonary rehabilitation and cease smoking.

Bullectomy

Patients considered for surgical treatment of bullous disease usually have large symptomatic (dyspnoea, bleed, pneumothorax). Due to the loss of elastic recoil in the bullous portion of lung, there is air trapping and expansion of the bulla. This leads to impairment of gas exchange and compression of relatively normal surrounding lung tissue. The ideal approach for bullectomy is VATS excision with a stapler either with or without buttressing of the staple line. Surrounding lung tissue is generally not normal and management of air leak and the pleural space in this group of patients is particularly important.

Lung transplantation

End-stage emphysema is the commonest condition for which lung transplantation is performed. Most patients are receiving supplemental oxygen therapy and the majority of patients are transformed by surgery with significant improvements in pulmonary function and exercise capacity. Lung transplantation however, is not an option for all due to the shortage of donor organs and the age restrictions applied. In addition the early post-operative mortality is relatively

high (~10%) with 5-year survival of ~50%. In addition, there is major morbidity associated with immunosupression regimens

LVRS

The premise behind LVRS is the removal of destroyed functionless lung to allow for better function of the remaining lung without the morbidity incurred by transplantation. It has been well documented that there are certain groups of patients who have been shown to benefit from LVRS. The procedure may be performed either as a bilateral procedure through a median sternotomy or bilateral VATS or a s a staged unilateral procedure.

NETT TRIAL

The National Emphysema Treatment Trial (NETT) randomized 1218 patients (3777 assessed) with moderate to severe emphysema to pulmonary rehabilitation followed by randomisation to medical therapy or bilateral lung volume reduction surgery (LVRS).

In 2001, patients with an FEV1 <20% predicted and either a homogenous pattern of emphysema or TLCO <20% predicted were deemed to be at low probability of functional benefit and high probability of surgical mortality and were excluded from further randomisation.

Entire cohort

90-day surgical vs. medical mortality 7.9 vs. 1.3%, p<0.001. No difference in mortality between VATS or sternotomy. However, no difference was detected in overall mortality during follow-up (mean 29.2 months) despite the higher initial operative mortality. The surgical group had increased exercise capacity vs. medical therapy. For the identified high risk patients (FEV1 <20% and homogenous emphysema or TLCO <20%) (n= 140), the 90-day mortality was 28.6% vs. 0% (surgery vs. medical.

Non-high risk patients (n= 1078)

The 30-day mortality was 2.2 vs. 0.2% and 90-day mortality 5.2 vs. 1.5% (surgical vs. medical, both p≤0.001). One month after randomisation 28.2% of surgical patients were hospitalized, rehabilitating or unable to answer follow-up but known to be alive vs. 2.2% of medical patients. These figures at 8 months converged to 3.3 vs. 3.7%. Changes in exercise capacity (6 minute

walk, predicted FEV1, quality of life and degree of dyspnoea) all favoured surgery at six, 12 and 24 months.

Predictors of outcome in non-high risk patients

The only baseline factors associated with differences in mortality were

1. Absence/presence of upper lobe predominance of emphysema
2. Baseline exercise capacity

- Upper lobe emphysema/low exercise capacity surgical patients had a lower risk of death (RR= 0.47), were more likely to have an improvement > 10W in maximal workload and in scores on quality of life questionnaire(QoLQ) at 24 months
- Upper lobe/high exercise capacity no difference in mortality, but improvements in workload and QoLQ at 24 months for surgical candidates.
- Non-upper lobe/low exercise capacity no difference in mortality or workload. Surgery patients had improved health related QoLQ scores at 24 months.
- Non-upper lobe/high exercise capacity, surgery patients had increased mortality vs. medical group and no difference in workload or QoLQ scores.

Long-term follow up

At a median 4.3 year follow-up in the NETT there was an overall survival advantage for LVRS vs. medical therapy (RR 0.86, p= 0.02).

Sub-groups as defined by NETT

- Upper lobe/low exercise – Surgical candidates had a markedly lower risk of death at 5 years (RR= 0.57, p= 0.01).
- Upper lobe/high exercise - No survival advantage. Improved exercise and increased QoLQ scores for surgical candidates.
- Non upper-lobe/low exercise – No survival advantage. Improvements of surgical patients in QoLQ scores disappeared over 3 years.
- Non-upper lobe/high exercise – Similar risk of death, equivalent workload and QoLQ scores.

Endo-bronchial valves

Endobronchial valves (EBVs) allow for egress of air from the portion of lung distal to their placement in the airway without allowing further inflation. Thereby having the potential to reduce lobar volume in patients with emphysema. Potential complications of EBVs include distal pneumonia and EBV expectoration/aspiration or dislodgement. The Endobronchial Valve for Emphysema Palliation Trial (VENT) screened 977 patients and randomised 321 (2:1, EBV:medical) to study the safety and efficacy of such an intervention following a period of pulmonary rehabilitation. Inclusion criteria: Heterogenous emphysema with an FEV1 15-45% predicted. TLC > 100% and RV > 150% predicted and post-rehabilitation 6-minute walk > 140m. Exclusion: giant bullae, previous thoracotomy, α1-AT deficiency, TLCO < 20% predicted.

Primary endpoints were change in FEV1 and distance on 6-minute walk. The primary safety end-point was a composite of six major complications at six months (death, empyema, massive haemoptysis, pneumonia distal to the EBV, pneumothorax, ventilator dependent respiratory failure >24h).

At 12-month follow up 19.1% of EBV and 27.7% of had missing data for the primary efficacy end-point.

At 6 months, there was an increase of 4.3% in the FEV1 in the EBV group (1 percentage point), as compared with a decrease of 2.5% (0.9 percentage point) in the control group (p= 0.005). On six minute walk, there was an increase of 9.3m (2.5%) vs. a decrease of 10.7m (3.2%) for EBV vs. medical therapy (p= 0.02 – distance and p= 0.04 percentage change).

At 90 days, in the EBV group, as compared with the control group, there were increased rates of exacerbation of chronic obstructive pulmonary disease (COPD) requiring hospitalization (7.9% vs. 1.1%, p=0.03) and haemoptysis (6.1% vs. 0%, p=0.01).At 6 months the rate of the composite six major complications was 6.1% vs. 1.2% (EBV vs. medical, p= 0.08) and at 12 months, the rate of the composite complications was 10.3% in the EBV group versus 4.6% in the control group (p=0.17 The rate of pneumonia in the target lobe in the EBV group was 4.2% at 12 months.

31 (14.5%) subjects required valve removal (between 1-377 days after insertion).

EBV therapy induced modest changes in PFTs and performance with more frequent exacerbations of COPD and haemoptysis post-implantation.

Further reading

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Thymoma

Mr PB Rajesh

Much of the management of thymoma is based on observational series with no randomised controlled trials. There is much debate in the literature with regard to

- How best to classify thymoma
- Optimal treatment including in which patients to use neo-adjuvant and adjuvant therapies
- The extent of resection and optimal approach
- Outcomes

The International Thymic Malignancy Interest Group (ITMIG) has recently been set up to provide infrastructure for international collaboration, promote a scientifically-based approach, and facilitate dissemination of knowledge about thymic malignancies and other mediastinal diseases.

http://www.itmig.org

Thymoma

Thymic malignancies are relatively uncommon, and have been characterized more by repeated dogma than actual data. In the last decade much data has been accumulated, but developing a composite body of knowledge is limited by differences in definitions and outcomes. Nevertheless, a clearer picture of management of these patients is emerging.

The majority of thymomas are indolent, however, they should not be considered benign as all have the ability to metastasise. One third are asymptomatic (incidental finding), one third are associated with myasthenia gravis and one third have systemic symptoms. 5-15%% of patients with myasthenia have a thymoma and 30-50% of patients with thymoma have myasthenia. Other autoimmune conditions associated with thymoma include red cell aplasia (2-5%) and hypogammaglobulinaemia (2-5%). They are the commonest anterior mediastinal tumour in females over 40 and in males between 40-70 years of age. Under the age of 40 they are less common, but increase in incidence with each decade of life.

Classification of thymoma

Masaoka classification

I	Macroscopically encapsulated, no microscopic capsular invasion
IIa	Microscopic transcapsular invasion into surrounding fatty tissue or mediastinal pleura
IIb	Macroscopic invasion of fatty tissue, must be microscopically confirmed
III	Macroscopic invasion into neighbouring organs
IVa	Pleural or pericardial metastases
IVb	Lymphatic or haematogenous metastases

WHO histological classification

A	Spindle epithelial cells, no atypia
AB	Spindle epithelial cells with foci of neoplastic lymphocytes
B1	Epitheliod cells, resembling cortex and medulla

B2 Epitheliod cells with scattered neoplastic cells

B3 Epitheliod cells with mild atypia

C Thymic carcinoma

Natural history

The majority have an indolent course, but they should not be considered benign as at presentation 10% have pleural or pericardial deposits and 35 and 6% nodal or distant metastases. When they recur, the vast majority do so with pleural or pericardial deposits (56%), distant metastases are present in 31% and 14% have nodal involvement.

Surgical resection

If CT is suggestive of thymoma, in the age groups above, with normal serum tumour markers, then for clinically stage I or II disease, some authorities feel that it is reasonable to proceed to formal resection without biopsy. If it is stage III then a biopsy is useful as neoadjuvant platinum based chemotherapy followed by surgical resection and adjuvant DXT may be appropriate in aggressive thymomas. Biopsy is also useful if the diagnosis is equivocal or potentially lymphoma. Performing a biopsy does not adversely predict survival and biopsy site seeding is extremely rare. FNA gives a yield of 60% and open biopsy 90%.

Operative mortality should be <2%.

Approaches

Sternotomy

VATS

Transcervical

Outcomes

Complete resection (R0) with invading structures, there is probably little benefit from debulking. R0 resection rates approach 100%, 88% and 49% for stages I, II and III respectively.

Ten year survival following resection approximate 90-100%, 75-94%, 56% and 38% for stages I-IV, respectively.

The presence of myasthenia is now not considered to be an adverse prognostic factor. Following surgical resection, patients should continue with their myasthenic regimens as the rate of remission is variable and only ~40% of patients at 5 years post resection are in complete remission.

Neo-adjuvant and adjuvant treatment

Neoadjuvant chemotherapy followed by surgery and DXT for stage III and Iva increases R0 resection and 5-year survival vs. surgery followed by DXT. NO role for post-operative DXT in R0 resected stage I and II disease and a questionable role in R0 stage III (meta-analysis data). Post-operative DXT is probably useful in the setting of an R1 resection.

Prognostic factors

Masaoka staging (I and II) is the most important prognostic factor followed by an R0 resection. WHO histological type does not appear to have a bearing on prognosis with the exception of thymic carcinoma (WHO type C) which has a poor prognosis. A diagnosis of myasthenia does not have a bearing on the prognosis.

Further reading

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Pulmonary metastasectomy: a moving target

Paul E. Van Schil

Surgical resection of lung metastases is a widely accepted procedure but due to local and distant recurrences reported 5-year survival rates are only 30 to 40%. Main prognostic factors are histological type and complete resection. Every patient has to be discussed within a multidisciplinary tumour board to determine optimal treatment. A better survival is reported in patients with a single metastasis and a disease-free survival of more than 3 years. Reoperations are feasible but often patients become inoperable due to insufficient pulmonary reserve and new treatment modalities are looked for. In some cases combined modality treatment is indicated. The maximal dose of intravenous chemotherapy is limited due to systemic side-effects, mainly haematological. As isolated limb and liver perfusion, isolated lung perfusion has the advantage of selectively delivering an agent into the lung while diverting the venous effluent. Other related methods of delivering high-dose locoregional chemotherapy include embolic trapping (chemo-embolization) and pulmonary artery infusion without control of the venous effluent.

Isolated lung perfusion has proven to be highly effective in experimental models of pulmonary metastases with a clear survival advantage. Lung levels of cytostatic drugs are significantly higher after isolated lung perfusion compared to intravenous therapy without systemic exposure. Phase I human studies have shown that isolated lung perfusion is technically feasible with low morbidity and without compromising the patient's pulmonary function. Further clinical studies are necessary to determine its definitive effect on local recurrence, long-term toxicity, pulmonary function and survival.

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Pulmonary Metastastectomy

Surgical resection of pulmonary metastasis has become a standard thoracic surgical procedure.

Although there is a great deal of surgical experience in performing metastastectomy the European Society of Thoracic Surgeons (ESTS)-Lung Metastastectomy Working Group (formed in 2006) concluded that the available evidence for pulmonary metastastectomy was largely formed from registry data (Pasterino et al., J Thorac Cardiovasc Surgery 1997) and case-series and do not meet the criteria of evidence based medicine. The working group carried out a survey of current practise among ESTS members and the results of the survey were published in the Journal of Thoracic Oncology in 2008. The survey was designed to inform about current patterns of practice and was not designed to give recommendations. The Working group published their final report in a supplement to the J Thor Oncology (Supp 2, Vol 5 No 6, June 2010): They concluded that the current level of evidence is too low to allow firm recommendations on pulmonary metastastectomy. They strongly endorsed Professor Tom Treasure's proposal for a randomised controlled trial (RCT) of the effectiveness of pulmonary metastastectomy in improving overall survival and quality adjusted survival in patients with colorectal cancer. This UK based RCT PulMiCC is currently recruiting.

Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. J Thorac Cardiovasc Surg. (1997);37-49. Pasterino U., Buyse M., Friedel G., Ginsberg J., Girard P., Goldstraw P., Johnston M., McCormack P., Pass H., and Putman J.

This paper was based on retrospective review of the large 'International Registry of Lung Metastasis' database. Pasterino's review of over 5,000 cases demonstrated that complete surgical excision of pulmonary deposits is often feasible with low morbidity and mortality. The paper published in 1997 identified prognostic factors associated with increased survival. The results indicated that complete surgical excision of all pulmonary deposits is often feasible and associated with low morbidity and mortality. They demonstrated a median survival of 35 months following complete resection versus a median survival of 15 months with incomplete resection. They concluded that metastastectomy is a potentially curative treatment.

Improved survival was associated with complete resection, a longer disease-free interval (time from initial diagnosis of primary to diagnosis of pulmonary metastasis), and a smaller number of pulmonary metastasis. The prognosis for patients with germ cell metastasis was better than that of epithelial, sarcoma or melanoma metastasis. They also concluded that the incidence of 'inadequate' pre-operative staging was high enough to recommend that open intra-operative exploration was necessary to adequately identify and resect all metastasis; surgical approach remains an area of controversy.

Pulmonary metastasectomy: a survey of current practice amongst members of the European Society of Thoracic Surgeons. Internullo E, Cassivi SD, Van Raemdonck D, Friedel G, Treasure T; ESTS Pulmonary Metastasectomy Working Group. J Thorac Oncol. 2008 Nov;3(11):1257-66

This survey of ESTS members had 146 complete responses from 29 countries. They reported areas of consistency and divergence between current thoracic practitioners. There was general agreement amongst members that pulmonary metastastectomy was not warranted in cases where the primary tumour is uncontrolled or where complete resection of the lung metastasis is unlikely. Areas of controversy included the surgical approach (open versus VATS) and the role of repeated metastastectomy.

Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial.Treasure T, Fallowfield L, Lees B. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S203-6J

The PulMiCC trial was launched in March 2010 and is designed to evaluate whether pulmonary metastastectomy in patients with colorectal cancer prolongs survival and to assess the positive or negative implications of that surgery on symptoms and quality of life.

The criteria for eligibility is that patients must be of a good risk for surgical intervention, the primary site is controlled, no other metastatic disease is present (or if there are liver metastasis they must be suitable for surgery or some other treatment modality) and the pulmonary metastasis are thought to be completely resectable. PulMiCC allows participating centres to exclude those patients where the clinical group managing the patient feel that the benefit of

metastastectomy to the patient is certain ie. if local clinical opinion is that the patient would clearly benefit from metastastectomy or clearly not benefit then they should not be included.

There are two phases to the trial. The first phase includes any necessary further investigation, liver resection and/or chemotherapy if appropriate. Patient are then reassessed and if it is still felt that they are suitable for randomisation then they are then consented to allocation to either continued active monitoring or pulmonary metastastectomy and continued active monitoring.

Further reading

- Imaging requirements in the practice of pulmonary metastasectomy. Detterbeck FC, Grodzki T, Gleeson F, Robert JH. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S134-9. Review
- The European Society of Thoracic Surgeons lung metastasectomy project. Van Raemdonck D, Friedel G. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S127-9
- What are the considerations in the surgical approach in pulmonary metastasectomy? Molnar TF, Gebitekin C, **Turna** A. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S140-4. Review
- Techniques used in lung metastasectomy. Venuta F, Rolle A, Anile M, Martucci N, Bis B, **Rocco** G. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S145-50. Review
- Locoregional therapy. Van Schil PE, Furrer M, **Friedel** G. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S151-4.
- Thoracic lymphatic involvement in patients having pulmonary metastasectomy: incidence and the effect on prognosis. García-Yuste M, Cassivi S, Paleru C. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S166-9
- Extending surgery for pulmonary metastasectomy: what are the limits? Migliore M, Jakovic R, Hensens A, Klepetko W. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S155-60. Review